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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/489,760	01/21/2000	Elsa A. J. M. Goulmy	4285us	6225

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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	17

DATE MAILED: 06/04/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Application	Applicant(s)
09/489,760	GOULMY ET AL.

Office Action Summary

Examiner	Art Unit
" Neon" Phuong Huynh	1644

-- The MAILING DATE of this communication app ars on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,9 and 20-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 9 and 20-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-5, 9 and 20-24 are pending.

2. In view of the amendment filed 3/4/02, the following rejections remain.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-5, 9 and 20-24 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) a peptide constituting a T-cell epitope of the minor Histocompatibility antigen HA-1 wherein the peptide consists of VLXDDLLEA (SEQ ID NO: 1), which is 9 amino acid residues in length where X represents a histidine or an arginine for diagnosing minor Histocompatibility antigen (HA-1) incompatibility between donor and recipient of bone marrow transplant using in vitro CTL assays (See pages 5, 7, 14-17, 25-26 of the specification), generation of VLHDDLLEA or VLRDDLLEA specific CTL *in vitro* for adoptive immunotherapy, **does not** reasonably provide enablement for (1) *any* peptide, (2) *any* immunogenic polypeptide, (3) *any* "analog" and (4) *any* "derivative thereof" having up to 15 amino acids constituting a T cell epitope obtainable from minor Histocompatibility antigen HA-1, said peptide "comprising" the sequence of SEQ ID NO: 1 or a "derivative thereof" having similar functional or immunological properties, wherein X represents a histidine or arginine, (4) *any* "vaccine" (5) *any* "pharmaceutical formulation" comprising said immunogenic polypeptide, or derivative thereof for preventing graft versus host disease or to treat any HA-1 related autoimmune disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims for the same reasons set forth in Paper No 10.

Applicants' arguments filed 3/4/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) applicants have amended claim 1, 2 and 9 to recite a peptide, an immunogenic polypeptide and an analog having up to 15 amino acids to further defined the claims, (2) the term "derivatives thereof having similar functional or immunological

properties" defines on page 10, lines 8-14 of the specification as any peptides which may be produced and which can include left or right turning residues and can be designed and/or generated by various methods known in the art such as peptide synthesis and replacement mapping followed by functional binding studies, (3) With respect to claims 4, 5 and 21-24, the office fails to acknowledge what is actually being claimed (i.e., a vaccine comprising an immunogenic polypeptide and a pharmaceutical composition comprising an immunogenic polypeptide and) and is instead focusing on what the claimed composition might be used for, in this case, preventing GvHD or treating HA-1 related autoimmune disease. The claims for a vaccine and pharmaceutical formulation should not require verification for disease treatment. By focusing on one potential use of the composition/formulation, the Office is not considering the enablement of the vaccine composition themselves, which used to stimulate an animal's immune response to a particular immunogen. (4) The specification teaches ex-vivo-generated HA-1 specific CTLs efficiently lysed leukemic cells derived from acute myeloid leukemia (AML) and acute lymphoid leukemia (ALL) patients; the HA-1 specific CTLs can be safely transferred to HA-1 positive patients after bone marrow transplant (BMT).

However, the specification fails to define what are the specific "functional or immunological properties" of any derivative or analog of SEQ ID NO: 1 being claimed. The issue here is not how to make any derivative or analog of peptide of SEQ ID NO: 1, but rather, whether the resulting peptide, polypeptide, analog and derivative thereof after modification would have the same structure and function as the claimed peptide of SEQ ID NO: 1, in turn, would be useful for a vaccine, or a pharmaceutical formulation for treating just any disease.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only two peptides of minor Histocompatibility antigen HA-1. The peptides are VLHDDLLEA (SEQ ID NO: 2) and VLRDDLLEA (SEQ ID NO: 5) wherein the peptides having a structure of nine amino acids in length for diagnosing incompatible minor

Histocompatibility antigen HA-1 associated with bone marrow transplant and generating HA-1 specific CTLs ex-vivo.

Other than the specific peptides mentioned above for diagnosing incompatible minor Histocompatibility antigen HA-1 associated with bone marrow transplant and ex-vivo generated HA-1 specific CTLs, the specification does not teach how to make and use *any* peptide, *any* immunogenic polypeptide, *any* analog and derivative thereof "having up to 15 amino acids" constituting a T-cell epitope obtainable from the minor Histocompatibility antigen HA-1 "comprising" the sequence VLXDDLLEA of SEQ ID NO: 1 having similar functional or immunological properties, wherein X represents a histidine or an arginine residue for a vaccine or a pharmaceutical formulation for treating *any* disease. The term "comprising" is open-ended. It expands the peptide, polypeptide, and analog thereof to include additional amino acid at either or both ends of SEQ ID NO: 1 to read on MHC class II peptide. However, the specification discloses only MHC class I peptide since the length of claimed peptide of SEQ ID NO: 1 is only 9 amino acids in length and the generation of HA-1 specific CTLs. Further, Given the indefinite number and type of additional amino acids, in addition to the amino acids which already recited in SEQ ID NO: 1, it is unpredictable which undisclosed peptide, polypeptide, analog and derivative thereof would have the same function as the claimed peptides of SEQ ID NO: 1, 2 and 5, let alone having the same structure.

Abbas *et al* (of record) teach that even a single amino acid differences in the peptide fails to bind to the T cell receptor or loss of T cell function or both (See page 130, Table 6-7, in particular). Likewise, even a single amino acid differences in the nanomeric peptide can have a drastic effect on binding as evidence by applicants' data (see Figure 4, in particular). Because of the indefinite number of amino acids that may be encompassed in the polypeptide of instant claims and there is no disclosure about the structure associated with functions of *any* polypeptide, it is not clear a polypeptide "comprising" SEQ ID NO: 1 would have similar functional or immunological properties as SEQ ID NO: 1.

Furthermore, there is no guidance in the specification as to which amino acid residues within the full length amino acid sequence that after substitution, deletion or insertion will retain both structure and function similar to SEQ ID NO: 1. Colman *et al* (of record) teach that even a single amino acid difference in an antigen can abolish the antibody-antigen interaction entirely (page 33, in particular). Given the lack of guidance and working examples, predicting what changes can be made to the peptide of SEQ ID NO: 1 that after substitution, deletion, insertion

and/or modification will retain both structure and have "similar immunological function" is unpredictable. Since the specification fails to provide guidance regarding which amino acid can tolerate change, it follows that the "analog" and "derivative thereof" that are structurally and functionally equivalent to SEQ ID NO: 1 is not enabled. It also follows that the "analog thereof" regardless whether it is has similar or antagonistic activity is not enabled.

In addition, the specification fails to provide any guidance and *in vivo* working examples as to whether a "vaccine" or a "pharmaceutical formulation" comprising the immunogenic polypeptide, derivative thereof, or analog thereof would prevent Graft versus Host disease or would be able to treat HA-1 related autoimmune disease.

By definition, a vaccine is a composition to induce a specific immunity that **prevent** or protect against a specific disease caused by a specific agent (See Fundamental Immunology, second edition, pages 987-988, in particular). One of the criteria for a vaccine is the levels of antibody (humoral immune response) before and after immunization and the success of vaccination is judged by the extent of increase in the level of HA-1 peptide specific antibody. The second criterion for a vaccine is the ability to induce tolerance in the HA-1 negative donor and thereby protect the HA-1 positive recipient upon receiving the organ from Graft versus host disease or induction of tolerance in the HA-1 negative recipient. A vaccine and/or a "pharmaceutical formulation" in the absence of *in vivo* data is unpredictable because (1) the peptide/polypeptide may be inactivated before producing an effect due to proteolytic degradation or immunological inactivation or the inherently short half-life of the peptide/polypeptide; (2) the peptide/polypeptide may not bind to the TCR, or may not reach the target area because, i.e. the peptide/polypeptide may not be able to cross the mucosa or the peptide/polypeptide may be adsorbed by fluids, cells and tissues where the peptide/polypeptide has no effect; and (3) other functional properties, known or unknown, may make the peptide/polypeptide unsuitable for in vivo therapeutic use, i.e. such as adverse side effects which prohibit the use of the peptide for inhibiting Graft versus host disease. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). Since there is no *in vivo* working examples in the specification as filed to demonstrate the effectiveness of using *any* peptide for preventing GVH, or treating HA-1 related autoimmune disease, it is not clear that a vaccine or a "pharmaceutical formulation" against Graft versus host disease treating HA-1 related autoimmune disease comprising said immunogenic peptide is enabled. In re wands, 858 F.2d at

737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary.

In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

5. Claims 1-5, 9 and 20-24 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention for the same reasons set forth in Paper No 10.

Applicants' arguments filed 3/4/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) applicants have amended claim 1, 2 and 9 to recite a peptide, an immunogenic polypeptide and an analog having up to 15 amino acids to further defined the claims, (2) the term "derivatives thereof having similar functional or immunological properties" defines on page 10, lines 8-14 of the specification as any peptides which may be produced and which can include left or right turning residues and can be designed and/or generated by various methods known in the art such as peptide synthesis and replacement mapping followed by functional binding studies, (3) With respect to claims 4, 5 and 21-24, the office fails to acknowledge what is actually being claimed (i.e., a vaccine comprising an immunogenic polypeptide and a pharmaceutical composition comprising an immunogenic polypeptide and) and is instead focusing on what the claimed composition might be used for, in this case, preventing GvHD or treating HA-1 related autoimmune disease. The claims for a vaccine and pharmaceutical formulation should not require verification for disease treatment. By focusing on one potential use of the composition/formulation, the Office is not considering the enablement of the vaccine composition themselves, which used to stimulate an animal's immune response to a particular immunogen. (4) The specification teaches ex-vivo-generated HA-1 specific CTLs efficiently lysed leukemic cells derived from acute myeloid leukemia (AML) and acute lymphoid leukemia (ALL) patients; the HA-1 specific CTLs can be safely transferred to HA-1 positive patients after bone marrow transplant (BMT).

The specification discloses only two peptides of minor Histocompatibility antigen HA-1. The peptides are VLHDDLLEA (SEQ ID NO: 2) and VLRDDLLEA (SEQ ID NO: 5) wherein the peptides having a structure of nine amino acids in length for diagnosing incompatible minor Histocompatibility antigen HA-1 associated with bone marrow transplant and generating HA-1 specific CTLs ex-vivo. The specification discloses only MHC class I peptides which are 9 amino acids in length.

The specification does not reasonably provide a **written description** of (1) *any* peptide, (2) *any* immunogenic polypeptide, (3) *any* "analog" and (4) *any* "derivative thereof" having up to 15 amino acids constituting a T cell epitope obtainable from minor Histocompatibility antigen HA-1, said peptide "comprising" the sequence of SEQ ID NO: 1 or a "derivative thereof" having similar functional or immunological properties, wherein X represents a histidine or arginine, (4) *any* "vaccine" (5) *any* "pharmaceutical formulation" comprising said immunogenic polypeptide, and derivative thereof for preventing graft versus host disease or to treat any HA-1 related autoimmune disease. With the exception of the specific peptides mentioned above, there is insufficient written description about the structure associated with function of (1) *any* peptide, (2) *any* immunogenic polypeptide, (3) *any* "analog" and "derivative thereof" having up to 15 amino acids mentioned above. Applicants have not described the types of an amino acids (neutral, hydrophobic, hydrophilic) to be added, substituted, deleted, and/or modified to arrive at a peptide or immunogenic polypeptide "comprising" the sequence of VLXDDLLEA that has similar functional or immunological properties or antagonistic immunological properties, in turn, for a "vaccine" or a "pharmaceutical formulation" for preventing any disease. Furthermore, an analog, antagonist, or derivative thereof may include protein, peptide, nucleic acid, carbohydrate, or organic molecule. Given the lack of a written description of *any* additional representative species of peptide, immunogenic polypeptide, analog and derivative thereof, a vaccine and a pharmaceutical formulation comprising said peptide, immunogenic polypeptide, analog and derivative thereof, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-5, 9 and 20-24 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the same reasons set forth in Paper No 10.

The phrase "having similar functional or immunological properties" as recited in claims 1, 2 and 9 renders the claims indefinite because the metes and bounds of the specific immunological properties are not defined. One of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention.

Applicants' arguments filed 3/4/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) the term "derivatives thereof having similar functional or immunological properties" defines on page 10, lines 8-14 of the specification as any peptides which may be produced and which can include left or right turning residues and can be designed and/or generated by various methods known in the art such as peptide synthesis and replacement mapping followed by functional binding studies.

However, the specification fails to define what are the specific "functional and immunological properties" of SEQ ID NO: 1.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1-2, 4-5, 9, 21 and 23 stand rejected under 35 U.S.C. 102(b) as being anticipated by Haan *et al* (of record, Eur J Immunol 26:2680-2685, 1996; PTO 892) for the same reasons set forth in Paper No 10.

Applicants' arguments filed 3/4/02 have been fully considered but are not found persuasive.

Applicants' position is that Haan disclosed non-isolated peptide sequences pertaining to a different minor Histocompatibility antigen.

However, a product is a product irrespective of how it is made. Further, claims 1 and 2 recite a "derivative thereof", while claim 9 recites "an analog" of SEQ ID NO: 1.

Haan *et al* teach chimpanzee HA-1 and HA-2 peptides which have the following sequence YXGEVXVSV and are 9 amino acids in length and these HA-1 and HA-2 peptides are assumed to be the derivative and analog of the claimed immunogenic polypeptide because they have similar functional or biochemical properties of the human HA-1 and HA-2 (See page 2683, column 1, paragraph 1, in particular). Claims 4-5, 21 and 23 are included in this rejection because the vaccine comprising the immunogenic polypeptide which is the derivative or analog of HA-1 and HA-2 that has the same structure and inherent immunological functional properties. Haan *et al* further teach the peptides are in HBSS buffer with 50mM Hepes (page 2682, column 1, 1st paragraph, in particular) which can be used as a pharmaceutical medium and the use of non-human primates as a model to study bone marrow transplantation-related reactivities such as GVHD and graft-versus leukemia reactions (See page 2684, in particular). Thus, the reference teachings anticipate the claimed invention.

10. The following new ground of rejection is necessitated by the amendment filed 3/4/02.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1-5, 9 and 20-24 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection**.

The "**up to** 15 amino acids" in Claims 1, 2 and 9 represents a departure from the specification and the claims as originally filed. The passages pointed out by applicant in the amendment filed 3/4/02 do not provide a clear support for the said phrase.

13. No claim is allowed.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

16. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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Patent Examiner
Technology Center 1600
June 3, 2002

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